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ORIGINAL RESEARCH ARTICLE

Hepatorenal dysfunction identifies high-risk patients with acute heart failure: insights from the RELAX-AHF trial

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Abstract

Aims Episodes of acute heart failure (AHF) may lead to end-organ dysfunction. In this post hoc analysis of the Relaxin in Acute Heart Failure trial, we used the MELD-XI (Model of End-Stage Liver Dysfunction) score to examine hepatorenal dysfunction in patients with AHF.

Methods and results On admission, the MELD-XI score was elevated (abnormal) in 918 (82%) patients, with 638 (57%) having isolated renal dysfunction (creatinine $>$ 1 mg/dL), 73 (6.5%) isolated liver dysfunction (bilirubin $>$ 1 mg/dL), and 207 (18.5%) coexisting dysfunction of the kidneys and the liver (both creatinine and bilirubin $>$ 1 mg/dL). The percentage of patients with elevated MELD-XI score remained constant through a 60 day follow-up, as we observed a gradual decrease of liver dysfunction prevalence, counterbalanced by an increase in renal dysfunction. Serelaxin treatment was associated with a lower MELD-XI score on Day 2 and Day 5 (both $P < 0.05$), but this difference vs. placebo disappeared during longer follow-up. In the multivariable model, an elevated MELD-XI score on admission was associated with higher 180 day mortality: hazard ratios (95% confidence interval) for cardiovascular death were 3.10 (1.22–7.87), and for all-cause death 2.47 (1.19–5.15); both $P < 0.05$. The addition of the MELD-XI score to a prespecified prognostic model increased the discrimination of the model for all-cause death, but the increment in the *C*-index was only modest: 0.013 ($P = 0.02$).

Conclusions In patients with AHF, hepatorenal dysfunction is prevalent and related to poor outcome. The MELD-XI score is a useful prognosticator in AHF.

Keywords Acute heart failure; Liver dysfunction; Kidney dysfunction; Prognosis; MELD-XI score

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Introduction

In the recent years, our understanding of the pathophysiology of acute heart failure (AHF) has evolved, but still, the key underlying mechanisms that can be efficiently targeted have not been identified.[1–3] It has been documented that each episode of acute decompensation may lead to dysfunction or injury of end-organs other than the heart, such as the kidneys, liver, brain, or lungs, with subsequent detrimental consequences.[4–11] Typically, though, interest has been focused on the assessment of each of these organs in isolation while evaluating patients with AHF, which is somehow surprising, as the dysfunction of several organs typically coexists in clinical practice. Further to this end, the cross-talk between the two

organs (the liver and the kidneys) whose function has a fundamental impact on the natural course of an episode of AHF (the liver and the kidneys)[12–15] has not been thoroughly investigated in this clinical syndrome.

Hepatorenal interaction can be assessed using the MELD (Model of End-Stage Liver Dysfunction) score that describes the function of these two organs. The score is calculated on the basis of creatinine and bilirubin values and was originally developed to assess the prognosis of patients with advanced liver disease.[16] Recently, it has been implemented in populations with heart disease including AHF.[17–21]

Serelaxin is a recombinant form of human relaxin-2, a peptide hormone that mediates cardiovascular and renal adaptations to pregnancy. In the recent RELAX-AHF (Relaxin in Acute Heart Failure) trial, early administration of serelaxin in patients with AHF was associated with fewer signs of organ damage.[22] This study is a post hoc analysis of patients enrolled into the RELAX-AHF trial in order to evaluate the prevalence and prognostic importance of hepatorenal dysfunction on the basis of the calculation of the MELD score. We also aimed to assess the impact of serelaxin on hepatorenal interaction.

Methods

Inclusion/exclusion criteria and study design

The RELAX-AHF was an international, double-blind, placebo-controlled trial that enrolled 1161 patients admitted to hospital for AHF who were randomly assigned within the first 16 h from presentation to receive 48 h intravenous infusions of either placebo (n = 580) or serelaxin 30 μg/kg per day (n = 581) on top of standard care. Detailed descriptions of the background and study design as well as the results of the main study have been published elsewhere.[22,23] For entry, patients were required to have dyspnoea, congestion confirmed on chest radiograph, increased brain natriuretic peptide (BNP $\geq$ 350 pg/mL) or N-terminal prohormone of BNP (NT-proBNP $\geq$ 1400 pg/mL), mild-to-moderate renal insufficiency [estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73 m^2], and systolic blood pressure $>$ 125 mmHg.

Further exclusion criteria relevant to the analyses were known, including severe renal impairment (eGFR $<$ 25 mL/min/1.73 m^2) and hepatic impairment [total bilirubin $>$ 3 mg/dL, or increased ammonia levels (if performed), or cirrhosis with evidence of portal hypertension such as varices]. Other exclusion criteria are outlined in the design paper.[23,24]

Clinical assessments of heart failure signs and symptoms were performed, and blood samples for laboratory assessments were drawn at baseline, 24 h (Day 1), 48 h (Day 2), Days 3–4 (if patient was still in hospital), and Days 5, 14, and 60. All laboratory tests were conducted in the central laboratory.

The RELAX-AHF trial fulfilled the requirements stated in the Declaration of Helsinki, and the protocol was independently approved by the ethics committee at each participating centre; written informed consent was obtained from each participant.

Model of End-Stage Liver Dysfunction excluding INR (MELD-XI) calculations

Originally, MELD was developed and validated to assess prognosis in patients with advanced liver disease awaiting liver transplant or transjugular intrahepatic portosystemic shunt procedure.[12,13] As the original MELD formula uses international normalized ratio (INR) values for risk stratification, it cannot be used in patients on vitamin K antagonists (oral anticoagulants). Thus, in this population, modification of the score excluding INR (MELD-XI) was developed by Heuman *et al*.[16] and used for these analyses: [5.11 × $\log_e$ bilirubin (mg/dL)] + [11.76 × $\log_e$ creatinine (mg/dL)] + 9.44. Following the recommendations of the United Network for Organ Sharing for liver transplant organ allocation in the USA and other authors, the lower limit of bilirubin and creatinine was set at 1.0 mg/dL (SI units: 17.1 and 88.4 μmol/L, respectively).[16] This correction is recommended to prevent negative scores, as the logarithms of values lower than 1.0 are negative. Thus, for the analysis, values of bilirubin or creatinine $<$ 1 mg/dL were assigned a value of 1 mg/dL when computing the MELD-XI score. As the logarithm of 1.0 equals 0, a value $<$ 1 mg/dL for either component does not impact the score. If both components are $\leq$1 mg/dL, the final score is 9.44 (the lowest possible); consequently, any score above that cut-off was considered elevated.

For the purpose of this analysis, and to be consistent with the definition of elevated MELD-XI, the cut-offs for organ dysfunction were defined by values of creatinine and bilirubin of 1 mg/dL; that is, patients with creatinine or bilirubin values $>$ 1 mg/dL were considered as having isolated kidney or liver dysfunction, respectively, or concurrent organ dysfunction, if both were elevated. Any MELD-XI score $>$ 9.44 points was considered elevated; thus, the study population was arbitrary dichotomized with the MELD-XI cut-off.

Endpoints of the present analysis

The primary and secondary endpoints of the RELAX-AHF trial are presented in previous papers.[23,24] The outcomes for this analysis were all-cause and cardiovascular mortality within 180 days from randomization.

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Statistical analyses

Continuous variables are reported as mean ± standard deviation for normally distributed variables and median (inter-quartile range) for non-normally distributed variables; categorical variables are reported as percentages. Differences in baseline characteristics between the subgroups of patients with a different status of kidney/liver dysfunction at baseline were tested for by using one-way ANOVA or Kruskal–Wallis rank test for continuous data and a χ^2 test for categorical data.

Individual MELD-XI scores were calculated at baseline and on Days 2, 5, 14, and 60 using the equation developed by Heuman *et al*. From this, the proportion of patients with an elevated MELD-XI score at each of these time points was calculated, and the individual contributors of an elevated MELD-XI score were assessed by calculating the proportion of patients with isolated liver dysfunction, isolated renal dysfunction, or coexisting dysfunction of kidneys and liver. Next, the pattern of change in MELD-XI score over time until Day 60 was assessed by fitting a linear mixed effects model to the longitudinal measurements taken at baseline and on Days 2, 5, 14, and 60. Missingness due to mortality events before Day 60 was accounted for in the analysis by jointly modelling the longitudinal process and the survival process. Differences in the mean trajectories of the MELD-XI score in the serelaxin and placebo groups were tested for by including interaction terms with the time components in the mixed effects model. Similar models were subsequently fitted to describe the average bilirubin and creatinine trajectories.

The association between the baseline MELD-XI score (both continuous and dichotomized into elevated/normal) and the outcomes of interest were assessed using Cox proportional hazards models. Both unadjusted models and models adjusted for previously established predictors of those outcomes (geographic region, systolic blood pressure, orthopnoea, angina, hyperthyroidism, mitral regurgitation, atrial fibrillation/flutter at screening, white blood cell count, lymphocyte %, blood urea nitrogen, sodium, potassium, calcium, total protein, NT-proBNP, high sensitive troponin T (hs-TnT), and study treatment for 180 day cardiovascular mortality; age, congestive heart failure within 1 month prior to randomization, history of stroke/cerebrovascular accident (CVA), respiratory rate, systolic blood pressure, peripheral oedema, orthopnoea, lymphocyte%, sodium, troponin T, and study treatment for 180 day all-cause mortality) were fitted. Next, to assess whether treatment with serelaxin modifies the effect of the MELD-XI score, interaction terms were added to both the unadjusted and adjusted models. Finally, the added predictive value of baseline MELD-XI score, creatinine, and bilirubin on top of the predictors included in the adjusted Cox models was assessed by calculating the change in Harrell's *C*-index as well as the continuous net reclassification improvement (cNRI). The cNRI is a category-independent metric that quantifies the amount of correct change in model-based predicted probabilities obtained by adding a biomarker to an established model. *C*-statistics was used to compare the goodness of fit of logistic regression models. In simple words, the higher the *C*-index, the higher the prognostic accuracy of the model. So the gain in *C*-index is related to improvement of the prognostic abilities of the model.

All patients with available MELD-XI score values at baseline were included in these analyses. Missing values for the other predictor variables were imputed with study treatment-specific median values. Similar analyses were additionally conducted for the individual components of the MELD-XI score (i.e. creatinine and bilirubin). *P*-values < 0.05 were considered to be statistically significant. All analyses were performed with R: A Language and Environment for Statistical Computing, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Prevalence of abnormal MELD-XI and its contributors at baseline and during follow-up

Among patients enrolled into the RELAX-AHF trial, 1120 had baseline creatinine and bilirubin data available, of whom

Table 1 Proportion of patients with elevated MELD-XI score and individual contributors (elevated creatinine only, elevated bilirubin only, and both) at prespecified time points

Time of evaluation	Elevated MELD-XI score	Isolated renal dysfunction	Isolated liver dysfunction	Coexisting hepatorenal dysfunction
Admission, % (n = 1120)	82.0 (918)	57.0 (638)	6.5 (73)	18.5 (207)
Day 2, % (n = 1092)	79.0 (863)	56.7 (619)	6.4 (70)	15.9 (174)
Day 5, % (n = 1058)	82.3 (871)	66.9 (708)	3.6 (38)	11.8 (125)
Day 14, % (n = 1036)	83.4 (864)	73.4 (760)	1.5 (16)	8.5 (88)
Day 60, % (n = 953)	79.5 (758)	69.0 (658)	2.8 (27)	7.7 (73)

Elevated MELD-XI score: MELD-XI score > 9.44. Isolated renal dysfunction: serum creatinine > 1 mg/dL (>88.4 μmol/L) with serum bilirubin ≤ 1 mg/dL (>17.1 μmol/L). Isolated liver dysfunction: serum bilirubin > 1 mg/dL with serum creatinine ≤ 1 mg/dL. Coexisting hepatorenal dysfunction–serum creatinine > 1 mg/dL and serum bilirubin > 1 mg/dL.

Table 2 Comparison of baseline characteristics in patients with different patterns of abnormalities contributing to elevated MELD-XI score

Variable	Normal MELD-XI score (n = 202)	Isolated renal dysfunction (n = 638)	Isolated liver dysfunction (n = 73)	Coexisting hepatorenal dysfunction (n = 207)	P-value
MELD-XI score	9.44 ± 0	13.68 ± 2.4	11.25 ± 1.3	15.71 ± 2.89	<0.0001
Age (years)	73.83 ± 10.73	72.31 ± 11.15	72.19 ± 8.11	69.77 ± 12.31	0.0027
Sex (male)	26.2 (53)	69.1 (441)	47.9 (35)	80.7 (167)	<0.001
Race (White)	98.5 (199)	93.9 (599)	98.6 (72)	92.3 (191)	0.0096
Weight (kg)	76.54 ± 18.69	83.31 ± 18.26	78.45 ± 14.35	85.2 ± 19.07	<0.0001
BMI (kg/m^2)	28.52 ± 6.03	29.65 ± 5.72	28.59 ± 5.05	28.93 ± 5.42	0.045
Systolic blood pressure (mmHg)	142.96 ± 16.32	143.11 ± 16.7	141.27 ± 13.1	139.09 ± 16.64	0.019
Diastolic blood pressure (mmHg)	78.02 ± 13.47	78.36 ± 14.49	80.14 ± 10.76	81.55 ± 14.89	0.025
Heart rate (b.p.m.)	81.55 ± 14.96	78.61 ± 14.85	82.7 ± 16.6	80.88 ± 14.1	0.014
Respiratory rate (breaths per minute)	22.34 ± 4.85	21.77 ± 4.52	21.89 ± 4.97	21.83 ± 4.49	0.51
Past HF hospitalization	20.8 (42)	35.3 (225)	30.1 (22)	42.5 (88)	<0.0001
Number of hospitalizations	1.3 ± 0.71	1.63 ± 1.26	1.5 ± 0.86	1.84 ± 1.68	0.17
LVEF, %	42.49 ± 14.13	39.41 ± 14.04	36.6 ± 14.4	33.26 ± 15.17	<0.0001
NYHA class 30 days before admission					0.098
I	1.6 (2)	3.4 (16)	0 (0)	2.4 (4)	
II	39.8 (51)	36.3 (173)	41.2 (21)	27.3 (45)	
III	39.8 (51)	43.7 (208)	45.1 (23)	57 (94)	
IV	18.8 (24)	16.6 (79)	13.7 (7)	13.3 (22)	
Hypertension	86.1 (174)	89.3 (570)	83.6 (61)	78.7 (163)	0.0014
Mitral regurgitation	27.2 (55)	30.4 (194)	32.9 (24)	38.6 (80)	0.071
Ischaemic heart disease	40.1 (81)	57.5 (367)	43.8 (32)	49.8 (103)	<0.0001
Implantable cardiac defibrillator	7.9 (16)	14.4 (92)	2.7 (2)	18.8 (39)	0.00038
Atrial fibrillation	51.5 (104)	47.8 (305)	63 (46)	61.4 (127)	0.0016
Congestive heart failure 1 month prior	64.4 (130)	75.5 (482)	69.9 (51)	80.7 (167)	0.0011
Atrial fibrillation at screening	39.6 (80)	36.8 (235)	53.4 (39)	51.2 (106)	0.00038
ACE inhibitor	58.9 (119)	55.3 (353)	54.8 (40)	47.8 (99)	0.14
Angiotensin receptor blocker	14.4 (29)	16.3 (104)	13.7 (10)	18.4 (38)	0.67
Beta-blocker	67.3 (136)	68 (434)	63 (46)	73.9 (153)	0.26
PO loop diuretic 30 days prior	22.3 (45)	33.9 (216)	28.8 (21)	32.9 (68)	0.018
Dyspnoea by VAS, mm	44.34 ± 18.89	44.37 ± 19.87	41.81 ± 19.84	42.99 ± 20.69	0.64
General well-being by VAS, mm	44.22 ± 18.33	44.63 ± 19.05	42.47 ± 19.76	44.48 ± 20.36	0.84
Dyspnoea on exertion	100 (200)	99.5 (630)	100 (71)	99.5 (201)	0.73
Orthopnoea	95 (192)	96.2 (613)	95.9 (70)	95.7 (198)	0.9
Oedema	71.8 (145)	79.9 (509)	80.8 (59)	81.2 (168)	0.064
Rales	95 (192)	95.6 (610)	94.5 (69)	91.8 (190)	0.2
Jugular venous pressure	69.5 (137)	76.7 (476)	69 (49)	79.2 (160)	0.063
Alanine transaminase, U/L	23 [16.25–33]	21 [15–31]	22 [16–35]	23 [17–33.25]	0.0073
Albumin, g/L	4 ± 0.42	4.02 ± 0.42	4.08 ± 0.44	4.02 ± 0.49	0.64
Aspartate transaminase, U/L	25 [20–34.25]	23 [19–32]	29 [23–35.75]	27 [23–36]	<0.0001
BUN, mmol/L	19.83 ± 7.22	29.9 ± 11.32	18.45 ± 5.23	30.22 ± 11.22	<0.0001
Creatinine, mg/dL	0.89 ± 0.11	1.47 ± 0.33	0.89 ± 0.12	1.43 ± 0.29	<0.0001
Bilirubin, mg/dL	0.55 ± 0.21	0.58 ± 0.21	1.48 ± 0.44	1.67 ± 0.74	<0.0001
Haemoglobin, g/dL	12.8 ± 1.59	12.54 ± 1.84	13.32 ± 1.99	13.29 ± 1.97	<0.0001
WBC, ×10/L	8.43 ± 2.93	8.24 ± 2.76	7.56 ± 2.66	7.83 ± 2.84	0.04
Potassium, mmol/L	4.11 ± 0.57	4.35 ± 0.61	4.01 ± 0.44	4.29 ± 0.75	<0.0001
Sodium, mmol/L	141.3 ± 3.35	140.97 ± 3.29	140.18 ± 4.16	140.23 ± 4.3	0.0054

(*Continues*)

Table 2 (continued)

Variable	Normal MELD-XI score (n = 202)	Isolated renal dysfunction (n = 638)	Isolated liver dysfunction (n = 73)	Coexisting hepatorenal dysfunction (n = 207)	P-value
Total cholesterol, mmol/L	171.11 ± 46.86	159.91 ± 44.75	151.63 ± 47.83	141.14 ± 37.72	<0.0001
Total protein, g/L	6.7 ± 0.65	6.8 ± 0.65	6.84 ± 0.6	6.85 ± 0.63	0.12
Triglycerides, mmol/L	92 [64–125]	98 [73–139.25]	73 [55–86]	82 [61.5–108.5]	<0.0001
NT-proBNP, pg/mL	4246 [2508–7814]	4633 [2596.75–9109.75]	4315 [2949–7835]	6345.5 [3466–10 486.75]	0.00018
hs-cTnT, μg/L	0.03 [0.02–0.05]	0.04 [0.02–0.06]	0.03 [0.02–0.03]	0.04 [0.02–0.05]	<0.0001

Normal MELD-XI score = 9.44. Isolated renal dysfunction: serum creatinine > 1 mg/dL with serum bilirubin ≤ 1 mg/dL. Isolated liver dysfunction: serum bilirubin > 1 mg/dL with serum creatinine ≤ 1 mg/dL. Coexisting hepatorenal dysfunction: serum creatinine > 1 mg/dL and serum bilirubin > 1 mg/dL. Data shown are as percentage (number), mean ± SD, median [Q25%–Q75%].
BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VAS, visual analogue scale.

918 (82%) had an elevated MELD-XI score. Again, any MELD-XI score above the minimal possible value (9.44 points) was considered elevated. The mean baseline MELD-XI score was 13.1 ± 3.01 points with no difference between the serelaxin and placebo groups. The major contributors to the elevated baseline score were isolated renal dysfunction in 638 patients (57%), coexisting dysfunction of kidney and liver in 207 (18.5%), and isolated liver dysfunction in 73 (6.5%) (*Table 1*). The percentage of patients with an elevated MELD-XI score remained fairly constant (at the rate of 80%) through a 60 day follow-up. We observed a gradual decrease of isolated liver dysfunction (from 6.5% at baseline to 2.8% on Day 60) and hepatorenal dysfunction (from 18.5% at baseline to 7.7% on Day 60), which was counterbalanced by an increase of the number of patients with isolated renal dysfunction (an increase from 57% at baseline to 69% on Day 60) (*Table 1*).

Characteristics of patients with hepatorenal dysfunction

Detailed baseline characteristics of the RELAX-AHF study population have already been presented.[23] A comparison of the baseline characteristics of patients with kidney, liver, and coexisting kidney and liver dysfunction is presented in *Table 2*. Patients with coexisting hepatorenal dysfunction, when compared with the rest of the population, were younger, were more likely to be men, and with previous history of heart failure. They also presented signs of more advanced heart failure with lower ejection fraction, lower baseline systolic blood pressure, higher NT-proBNP, and more often biventricular pacemaker implanted (all $P < 0.05$) (*Table 2*). Interestingly, patients with hepatorenal dysfunction, when compared with the rest of the group, did not differ with respect to most clinical signs on admission.

Trajectories of MELD-XI and its contributors through Day 60 in the serelaxin and placebo groups

The average trajectories, estimated from the joint longitudinal–survival models, showed significant differences between the serelaxin and placebo groups with respect to changes in the MELD-XI score (interaction $P < 0.001$) and creatinine (interaction $P < 0.001$), but not bilirubin (interaction $P = 0.076$), through Day 60. The mean MELD-XI score and creatinine value decreased in the serelaxin group and increased in the placebo group during the first 2 days but were similar in the two groups by Day 14 and through Day 60 (*Figure 1*). Patients receiving serelaxin had a significantly lower mean MELD-XI score, and consequently, fewer patients had an elevated score, than had the placebo group on Day 2 and Day 5 (12.8 ± 3.13 vs. 13.5 ± 3.36 and 13.44.8 ± 3.44 vs. 13.97 ± 3.60, respectively, both $P < 0.05$), but this difference was no longer evident in a 60 day follow-up (*Table 3*, *Figure 2*).

Prognostic significance of hepatorenal dysfunction

There were 84 (7.2%) cardiovascular deaths and 102 (8.4%) all-cause deaths through Day 180. After multivariable adjustment, an elevated baseline MELD-XI score was associated with higher 180 day cardiovascular as well as all-cause mortality hazard ratio (HR) (95% CI) of 3.1 (1.22–7.87) and HR (95% CI) of 2.47 (1.19–5.15), respectively, both $P < 0.05$ (*Table 4*). Analogously, when the score was analysed as a continuous predictor, we found it to be significantly related to both prespecified outcomes: for CV death, HR (95% CI) of 1.14 (1.08–1.21) and for all-cause death HR (95% CI) of 1.11 (1.04–1.17), respectively (both $P < 0.05$) (*Table 4*). Patients with coexistence of liver and kidney dysfunction had significantly worse outcome than had the rest of the population;

Figure 1 Bar graphs representing the proportion of patients with an elevated MELD-XI score and individual contributors (elevated creatinine only, elevated bilirubin only, and both) at each of the prespecified time points in placebo vs. serelaxin treatment groups (*$P < 0.05$, **$P < 0.001$).

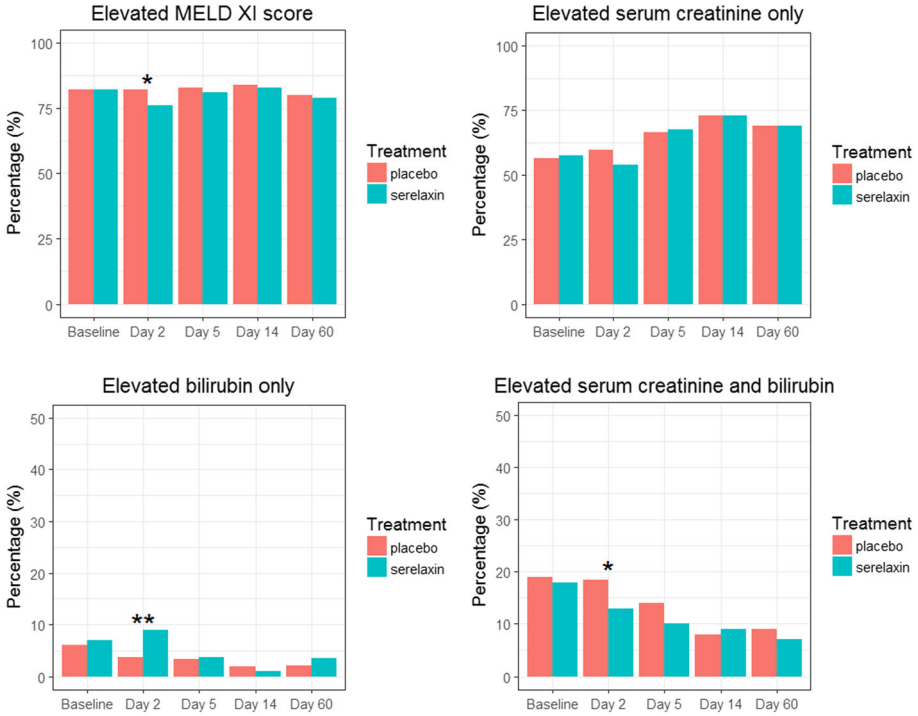

Table 3 Mean (SD) values of MELD-XI score at prespecified time points in all patients and comparison of the MELD-XI score in groups stratified by study treatment

Time point	Mean ± SD values of MELD at prespecified time points			
	All patients	Placebo	Serelaxin	*P*-value
Baseline	13.13 ± 3.01	13.11 ± 2.99	13.16 ± 3.03	0.800
Day 2	13.15 ± 3.26	13.5 ± 3.36	12.8 ± 3.13	0.0004
Day 5	13.71 ± 3.53	13.97 ± 3.60	13.44 ± 3.44	0.015
Day 14	13.84 ± 3.56	13.87 ± 3.44	13.81 ± 3.68	0.800
Day 60	13.37 ± 3.39	13.34 ± 3.27	13.39 ± 3.52	0.830

the HR (95% CI) for cardiovascular death and for all-cause death was 5.05 (1.85–13.76) and 4.24 (1.91–9.4), respectively, both $P < 0.05$.

Interaction analysis between study treatment, baseline MELD-XI, and its contributors

In general, interaction analyses showed no significant differential effect of study treatment on 180 day mortality in patients with different organ dysfunction profiles (all $P > 0.05$) (*Table 5*). Only the group without coexistence of hepatorenal dysfunction had significantly lower risk of mortality when treated with serelaxin than had the rest of the population ($P = 0.046$ for interaction).

Additive prognostic importance of hepatorenal dysfunction in acute heart failure

We tested the prognostic value of organ dysfunction over that provided by the baseline characteristics in a prespecified multivariable model.[25,26] The addition of either creatinine or bilirubin to the prespecified model did not result in a significant gain of the model's prognostic power (*Table 6*). Only the addition of either MELD-XI or hepatorenal dysfunction to the model increased the model's discrimination for all-cause death; however, the gain in the *C*-index was only modest: 0.013 and 0.010, respectively (both $P < 0.05$) (*Table 6*).[25,26]

Discussion

There are important messages in this post hoc analysis of the RELAX-AHF trial. Firstly, we found that a dysfunction of two organs—the liver and kidney—is prevalent in patients with AHF, as ~80% of the population had an elevated MELD-XI score, signifying dysfunction of at least one organ, close to the time of admission, and it remained prevalent until Day 60. This high prevalence may be partially related to the design of the RELAX-AHF trial, which included patients with decreased eGFR (in the range of 25–75 mL/min/1.73 m^2), so renal dysfunction was the main contributor to an elevated MELD-XI score.

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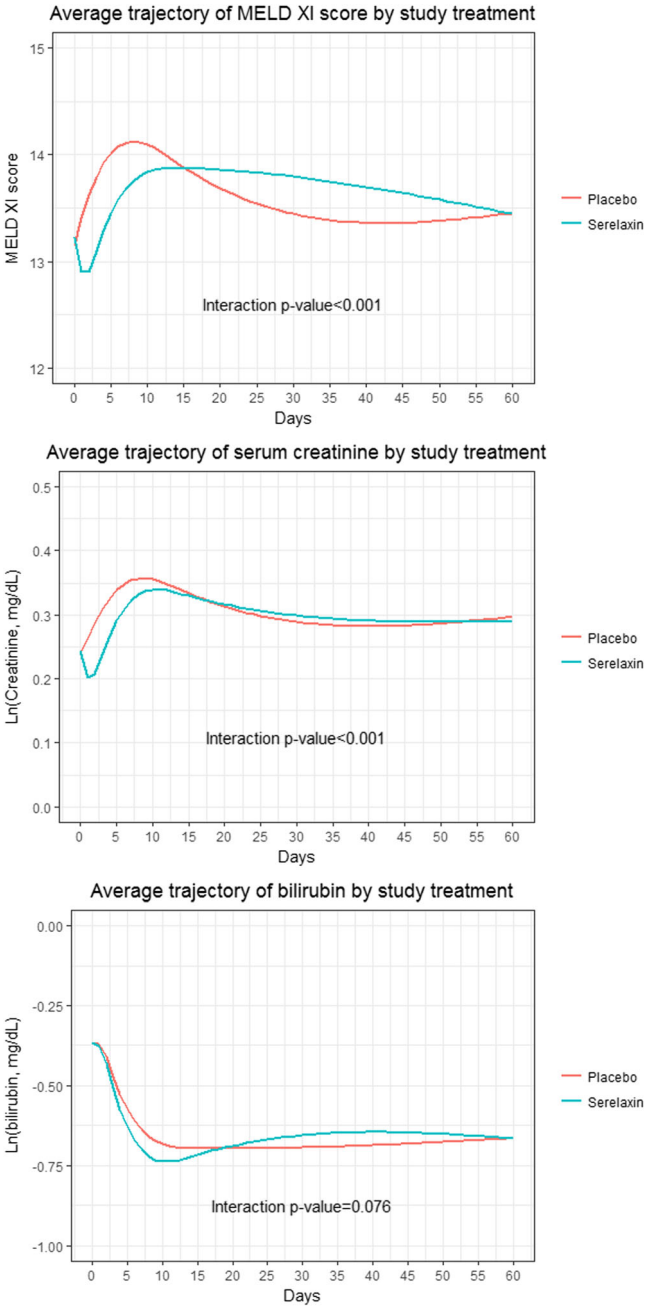
Figure 2 Average trajectories (based on the fixed effects of the longitudinal component of the joint model) of MELD-XI score, creatinine, and bilirubin over time in placebo vs. serelaxin treatment groups; interaction *P*-value indicates statistical significance of differences in the trajectories of the markers in the placebo vs. serelaxin treatment groups.



Importantly, though, we observed coexistence of liver and kidney dysfunction to be commonly present on admission (18.5% of all patients) with a gradual decrease over time. Still, however, ~10% of the trial population demonstrated evidence of liver dysfunction on both Days 14 and 60. One would expect intuitively that dysfunction of both organs would be frequent only in patients with overt signs of hypoperfusion and/or low blood pressure. Surprisingly, we revealed that end-organ dysfunction can be prevalent even in AHF patients with normal/high blood pressure (as ~18.5% of patients had both liver and kidney affected). Thus, the score could be used in the whole spectrum of heart failure patients, even without over clinical signs of multiorgan dysfunction.

Secondly, we found that patients with concurrent hepatorenal dysfunction had very unfavourable prognosis. We have demonstrated that any elevation of MELD-XI

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Table 4 Prognostic significance of hepatorenal dysfunction (MELD-XI score and its contributors) in RELAX-AHF population

	Time to cardiovascular death through Day 180				Time to all-cause death through Day 180			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[b]	
Predictor	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Elevated MELD-XI score (yes vs. no)	3.62 (1.47–8.95)	0.005	3.10 (1.22–7.87)	0.017	2.70 (1.31–5.56)	0.007	2.47 (1.19–5.15)	0.015
MELD-XI score, continuous (points)	1.16 (1.09–1.23)	<0.001	1.09 (1.02–1.16)	0.007	1.14 (1.08–1.21)	<0.001	1.11 (1.04–1.17)	<0.001
Creatinine, continuous (mg/dL)	4.54 (2.11–9.76)	<0.001	2.49 (1.08–5.73)	0.033	4.16 (2.07–8.37)	<0.001	2.85 (1.43–5.65)	0.003
Bilirubin, continuous (mg/dL)	1.68 (1.19–2.36)	0.003	1.71 (1.20–2.46)	0.003	1.53 (1.12–2.09)	0.007	1.58 (1.14–2.20)	0.006

HR should be interpreted per one-unit increment for continuous predictors; creatinine and bilirubin were natural-log transformed.
[a]Adjusted for geographic region, systolic blood pressure, orthopnoea, angina, hyperthyroidism, mitral regurgitation, atrial fibrillation/flutter at screening, white blood cell count, lymphocyte %, sodium, potassium, calcium, total protein, log2 NT-proBNP, log2 hs-cTnT, and study treatment.
[b]Adjusted for age, congestive heart failure within 1 month prior to randomization, history of stroke/CVA, respiratory rate, systolic blood pressure, peripheral oedema, orthopnoea, lymphocyte %, sodium, log2 hs-cTnT, and study treatment.

Table 5 Effect of serelaxin on time-to-event outcomes in patients with elevated vs. non-elevated baseline MELD-XI score and its components—an interaction analysis

	Time to cardiovascular death through Day 180			Time to all-cause death through Day 180		
	Elevated variable[a]			Elevated variable[a]		
Variable	No HR (95% CI)	Yes HR (95% CI)	Interaction *P*-value	No HR (95% CI)	Yes HR (95% CI)	Interaction *P*-value
MELD-XI score > 9.44	1.58 (0.26–9.44)	0.59 (0.38–0.93)	0.290	1.75 (0.42–7.40)	0.57 (0.38–0.87)	0.130
Creatinine > 1 mg/dL	0.84 (0.25–2.74)	0.60 (0.38–0.96)	0.620	1.00 (0.35–2.86)	0.58 (0.38–0.89)	0.350
Bilirubin > 1 mg/dL	0.46 (0.26–0.84)	0.98 (0.50–1.91)	0.100	0.53 (0.31–0.88)	0.83 (0.44–0.57)	0.270
Kidney and liver dysfunction	0.46 (0.26–0.81)	1.18 (0.56–2.48)	0.046	0.52 (0.32–0.96)	0.96 (0.49–1.91)	0.150

HR represents the hazard ratios for the effect of serelaxin treatment in subgroups of patients defined based on MELD-XI score, creatinine, and bilirubin; kidney and liver dysfunction represents both serum creatinine and bilirubin > 1 mg/dL.
[a]MELD-XI, creatinine, bilirubin, or kidney and liver dysfunction, where appropriate (according to the rows).

defined as being above the minimal value (which is 9.44 points) had prognostic significance. Interestingly, the analyses showed that isolated organ dysfunction, defined by a cut-off of 1 mg/dL for serum creatinine and bilirubin, has a much weaker prognostic significance, as only isolated liver dysfunction was associated with a higher risk of 180 day cardiovascular death. This may be seen as somehow unexpected, because renal dysfunction, defined as elevated creatinine, is a well-established prognosticator in heart failure, in both chronic and acute settings. In our study, patients who presented dysfunction of both organs on admission had a much higher risk of both all-cause and cardiovascular death, than had particularly those with a normal MELD-XI (four-fold to five-fold increase). This observation goes with agreement with recently published data, in which AHF patients presenting with higher number of dysfunctional/injured organs on admission had much worse outcome, than had those with lower numbers or no signs of dysfunction.[27] Analogically to present analyses, the dysfunction of two organs (kidney, liver, or heart) was related to 3.5-fold higher 1 year mortality.[27] Co-existence of hepatorenal dysfunction identified patients with more advanced heart failure (as evidenced by lower ejection fraction, lower systolic blood pressure, higher NT-proBNP, higher rate of history of chronic heart failure, and higher rates of oedema), but the association with poor outcomes remained highly statistically significant after multivariable adjustment. Importantly, there were no obvious clinical signs identifying patients with hepatorenal dysfunction on admission. This group of patients may be more prone to organ injury or experience more profound haemodynamic, metabolic, or neurohormonal disturbances leading to multiorgan dysfunction that cannot be detected by simple clinical examination. There is growing evidence on several vasoactive molecules such as nitric oxide, endothelin, adenosine, prostaglandins, and endotoxins that can affect not only systemic but also splanchnic circulation and, therefore, promote organ dysfunction in heart failure settings. Moreover, sympathetic tone, volume status, and intraabdominal pressure affect organ perfusion pressure, which is crucial for its optimal function. We believe that organ dysfunction in AHF is most likely a result of concurrence of several mechanisms, rather than the effect of one.[28,29] We can include among them

Table 6 Added prognostic value of baseline MELD-XI score and individual components on top of prespecified baseline models[a]

Variable	Time to cardiovascular death through Day 180				Time to all-cause death through Day 180			
	C-index (95% CI)	Gain in C-index	cNRI (95% CI)	*P*-value	C-index (95% CI)	Gain in C-index	cNRI (95% CI)	*P*-value
MELD-XI score	0.636 (0.57–0.70)	—	—	—	0.623 (0.57–0.68)	—	—	—
Creatinine	0.614 (0.56–9.67)	—	—	—	0.609 (0.57–0.65)	—	—	—
Bilirubin	0.591 (0.53–0.65)	—	—	—	0.576 (0.52–0.63)	—	—	—
Kidney and liver dysfunction	0.579 (0.53–0.62)				0.574 (0.53–0.62)			
Prespecified model	0.801 (0.76–0.86)	—	—	—	0.757 (0.71–0.80)	—	—	—
MELD-XI score + prespecified model	0.808 (0.76–0.86)	0.007	0.38 (−0.10 to 0.60)	0.073	0.770 (0.73–0.81)	0.013	0.35 (0.07–0.57)	0.020
Creatinine + prespecified model	0.803 (0.75–0.85)	0.002	0.25 (−0.14 to 0.49)	0.173	0.766 (0.72–0.81)	0.009	0.28 (−0.05 to 0.48)	0.066
Bilirubin + prespecified model	0.811 (0.76–0.86)	0.010	0.31 (−0.01 to 0.58)	0.060	0.763 (0.71–0.81)	0.006	0.22 (−0.05 to 0.47)	0.100
Kidney and liver dysfunction + prespecified model	0.810 (0.76–0.86)	0.009	0.29 (−0.08 to 0.51)	0.106	0.768 (0.72–0.81)	0.010	0.34 (0.07–0.55)	0.020

[a]Prespecified models include geographic region, systolic blood pressure, orthopnoea, angina, hyperthyroidism, mitral regurgitation, atrial fibrillation/flutter at screening, white blood cell count, lymphocyte %, sodium, potassium, calcium, total protein, log2 NT-proBNP, log2 hs-cTnT, and study treatment for time to cardiovascular death through Day 180; age, congestive heart failure within 1 month prior to randomization, history of stroke/CVA, respiratory rate, systolic blood pressure, peripheral oedema, orthopnoea, lymphocyte%, sodium, log2 hs-cTnT, and study treatment for time to all-cause death through Day 180.

low cardiac output (forward failure; however, it seems to have marginal role), low organ perfusion (the difference between mean arterial pressure and central venous pressure), lactate accumulation, activation of adrenergic drive, tricuspid valve insufficiency, right ventricle failure (backward failure), elevated central venous, and intraabdominal pressure.[29–35] Among them, congestion and central venous pressure seem to play a crucial role.[36] Indeed, in RELAX, patients with coexistence of renal and liver dysfunction had some signs of more advanced heart failure and congestion (refer to previous discussion).

The mean MELD-XI score in the RELAX-AHF trial was 13 points. Other authors have reported the mean score in AHF populations to be between 10 and 15 points.[17,21,37] We have demonstrated that the score remained fairly unchanged during the hospital stay as well as during the post-discharge phase until Day 60. However, we observed a gradual decrease in patients with isolated liver dysfunction and hepatorenal dysfunction, which was counterbalanced by an increase in the percentage of those who demonstrated isolated kidney dysfunction. This observation seems somehow counterintuitive to the traditional view of organ dysfunction in AHF, as we believe that mechanisms leading to or underlying decompensation of heart failure may also lead to functional deterioration of other organs.[27] Thus, one would rather expect the number of patients with organ dysfunction to decrease during the post-discharge phase.

Metra *et al*. have already shown an analysis of organ function during the serelaxin infusion phase of RELAX studies.[22] However, we present the problem (of multiorgan dysfunction in AHF) from a slightly different perspective. Firstly, we have shown a longer follow-up of the organ function (up to Day 60). This turned out to be a crucial, as the improvement of creatinine was only limited to the phase of active drug infusion. Secondly, we have provided the data of creatinine, bilirubin, and MELD-XI as continuous and categorized variables, whereas previous paper showed only categorized data.[22] Thirdly, we think the MELD-XI score is a unique marker that may combine the information of both organ (liver and kidney) dysfunction, while Metra had shown an analyses of each organ in separation. We believe that the interplay between organ dysfunction may identify patients at highest risk of adverse outcome in heart failure.

Additionally, we analysed the trajectories of creatinine, bilirubin, and MELD-XI over time and found that the differences are related to therapy. Patients who received serelaxin experienced a mean decrease in creatinine, but no changes in bilirubin, during the first 48 h (i.e. during drug infusion), which resulted in a decrease in mean MELD-XI score. After active therapy discontinuation, the trajectories of creatinine and MELD-XI became similar in the serelaxin and placebo groups (*Figure 2*). Interestingly, patients with both organs affected experienced the most obvious organ

protective benefits of the treatment. The difference in percentage of patients with elevated MELD-XI at Day 2, between placebo and serelaxin groups, was driven by a decrease of percentage of patients with both organs affected, which was counterbalanced by an increase of patients with elevated bilirubin alone (*Figure 1*). These findings confirm the previous observation that serelaxin demonstrated end-organ protective effects in AHF, but most likely, it was restricted only to a period of active drug infusion.[22] Moreover, we can only speculate that impermanent effect of the serelaxin on organ dysfunction may be one of the reasons that there was no impact on mortality in the RELAX study.[23,25]

Lastly, the biological importance of kidney and liver function is far more complex than can be assessed by measurement of creatinine and bilirubin. Thus, novel and promising markers of organ dysfunction as a result of heart failure severity have been proposed, like the assessment of liver stiffness (a marker related to congestion and liver remodelling as a result of congestion), assessment of urine sodium (a marker of renal water–sodium handling in heart failure), or serum osmolarity.[38–41] In the future, we will probably use a multimarket approach to assess a single organ as well as interplay between organs.

Study limitations

As this is a post hoc analysis of a population included in a clinical trial, it may not describe the scale of the problem of liver and kidney dysfunction in the whole spectrum of unselected AHF patients. On the one hand, the inclusion criteria resulted in an overestimation of the number of patients with an elevated MELD-XI (due to kidney dysfunction); on the other hand, the exclusion criteria eliminated patients with profoundly elevated bilirubin (>3 mg/dL) and creatinine (with eGFR < 25 mL/min/1.73 m^2). The limited number of deaths in patients with a normal MELD-XI score (i.e. <9.44 points) of 5 (0.4%) cardiovascular and 8 (0.68%) and all-cause deaths is another important limitation of the presented data.

Conflict of Interest

G.C., B.A.D., G.M.F., G.F., B.G., M.M., T.S., J.R.T., A.A.V., P.P. were members of executive/steering committee of RELAX AHF study, which was sponsored by Novartis. C.G. and T.S. are Novartis employees.

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